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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/591,653

09/05/2006

Hitoshi Ikeya

IKEYA=1

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EXAMINER

GALLIS, DAVID E

ART UNIT

PAPER NUMBER

1625

MAIL DATE

DELIVERY MODE

06/23/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/591,653	Applicant(s) IKEYA ET AL.	
	Examiner DAVID E. GALLIS	Art Unit 1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 March 2010.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1 through 17 are pending. Claims 1 through 8 and 10 through 17 have been amended. Applicants' claim to foreign priority from JAPAN 2004-062616 filed March 5, 2004 is acknowledged. Applicants' amendments and arguments filed March 10, 2010 has been entered and carefully considered.

2. With regard to the prior rejection of claims 1 through 17 under 35 U.S.C. 103(a), Applicants argue that Snow et al., while teaching polysaccharide conjugates, teach no methotrexate analogs linked by peptides to hyaluronic acid, and that Nogusa et al. teach direct hyaluronic acid conjugate with a different drug than methotrexate. Applicants' arguments are not found persuasive for reasons of record, however a new rejection under 103(a) has been crafted using new art against these claims (see below).

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 1 through 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tamura et al. (EP1082963, March 14, 2001, cited by Applicants) and Snow et al. (WO 94/13327, June 23, 1994, Cited by Applicants), and in further view of Nogusa et al. (US 5,688,931, November 18, 1997).

5. Claims 1 through 9 and 12 through 17 are drawn to a hyaluronic acid-methotrexate conjugate, a composition containing such and a therapeutic drug containing

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such, wherein methotrexate is conjugated with a carboxyl group of hyaluronic acid, a hyaluronic acid derivative, or a salt thereof through a linker containing a peptide chain consisting of 1 to 8 amino acids. Said linker is further limited to contain a C₂₋₂₀ alkylenediamine chain and the hyaluronic acid is 600,000 daltons. Claim 10 is drawn to compounds of formulas (V_a) and (V_b). Claim 11 is drawn to a process for producing the hyaluronic acid-methotrexate conjugate of claim 1.

6. Claims 1 through 17 are obvious over Tamura et al. and Snow et al. both teaching conjugated methotrexate systems. Tamura et al teaching matrix metalloprotease inhibitors and therapeutic agents (of which methotrexate is included. See page 6, line36) conjugated to hyaluronic acid by spacers (linkages) of various structure, some with peptide characteristics. Furthermore, Tamura et al. teach the same medicinal use of the methotrexate-hyaluronic acid conjugate as that which is instantly disclosed (see page 5, ¶0030). Snow et al. teach methotrexate analogs comprising peptide linkages conjugated to a ligand or chelate (see page 42, Scheme 4 and page 11, line 33). An intermediate taught by Snow et al. is instant formula (V_b) containing L₁ of formula (X'). Snow et al. also teaches their linkage group to include a 5 carbon alkylene group bridging two amine functionalities. While Tamura et al. do not teach a linkage that is specifically a peptide, Snow et al. remedies this deficiency by teaching a peptide linkage to methotrexate, and in further view of Nogusa et al. who teach a peptide-hyaluronic acid conjugate (see columns 24 and 25, EXAMPLES 20 through 22). Snow et al. teach the general procedure for preparation of a methotrexate-peptide system (see page 63 example 5) and Nogusa et al teach the preparation of hyaluronic

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acid-peptide systems (see EXAMPLES 20 through 22). It would be obvious to one of skill in the art to combine the teachings of Snow et al. and Nogusa et al. with that of Tamura et al. to produce a methotrexate-peptide-hyaluronic acid conjugate.

Furthermore, combining these syntheses to produce a system with the potential synergy of hyaluronic acid and methotrexate would be an obvious effort to one of skill in the art with a high probability of success.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David E. Gallis whose telephone number is 571-272-9068. The examiner can normally be reached on Mon-Thur 8:30-7:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on 571-272-1600. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Janet L. Andres/

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Supervisory Patent Examiner, Art Unit 1625

David E. Gallis
Patent Examiner